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Docket No. SHE0081.00

## **REMARKS**

### **I. Introductory Comments**

Based on the Advisory Action mailed on September 8, 2005, it appears that the Examiner will remove all the 35 U.S.C. §112 rejections upon entry of the present amendment (which includes each amendment presented in Applicants' August 16, 2005, Amendment). Applicants respectfully request, however, a formal indication from the Examiner in the next communication that these rejections have been removed.

In view of the Advisory Action mailed on September 8, 2005, it appears that the rejections remaining are as follows (notwithstanding Applicants' August 16, 2005, Amendment): under 35 U.S.C. §102(b) as allegedly being anticipated by Minamino et al. (U.S. Patent No. 6,037,452) (claims 1-7, 12-15, 17-22, 24, and 26-30); under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Davis et al. (U.S. Patent No. 4,179,337) (claims 1, 3-4 and 8-10); under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Greenwald (U.S. Patent No. 5,298,643) (claims 1, 3-4 and 8-11); under 35 U.S.C. §103(a) as allegedly being unpatentable over Röstin et al. [Röstin et al. (2000) *Bioconjugate Chem.* 11:387-396] in view of Greenwald (U.S. Patent No. 5,298,643) (claims 1, 14 and 16); and under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Longenecker et al. (U.S. Patent No. 4,994,439) (claims 1, 23 and 25).

As set forth in the Advisory Action mailed on September 8, 2005, Applicants understand that the Examiner has taken the position that "the previous rejections also apply to newly added claim 61." For purposes of this Submission, Applicants urge that the subject matter encompassed by new claim 61 is patentable for at least the reason provided herein with respect to the patentability of claim 3 (the claim to which new claim 61 depends).

### **II. Amendments to the Claims**

Claims 1-30 were previously pending and claims 31-61 were withdrawn from consideration without prejudice. As provided in Section I above, all claims have been amended or withdrawn. New claim 62 has been added.

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Support for the changes to the claims is identified below. Additional support other than that identified below may exist in the originally filed application for one or more changes to the claims.

Claim 1 has been amended to recite a conjugate comprising one, two or three water-soluble polymers covalently attached to a Factor VIII moiety. Support for a conjugate comprising one, two or three water-soluble polymers is found throughout the originally filed specification and claims. See, for example, Paragraphs 0121, 0123 and 0124. The conjunction "or" makes clear that -- with respect to water-soluble polymers -- *only* one, two *or* three water-soluble polymers are covalently attached to the Factor VIII moiety. In addition, the previously added phrase "wherein at least about 82% of conjugates in the composition" has been deleted; originally filed claim 1 supports subject matter not reciting this claim element.

Claim 1 has also been amended to change the lower value in the recited range from "greater than 5,000" to -- 6,000 --. Support for a lower value of 6,000 for the nominal average molecular weight range finds support in Paragraph 0080.

Claims 2-18 and claims 26-30 have been amended to recite a "conjugate" in view of the amendment to claim 1 to provide correct antecedent basis.

Claim 14 has been amended to delete (without prejudice) reference to "deletion variants, substitution variants or addition variants."

The dependencies of claims 19-25 have been amended in view of new claim 62.

New claim 62 has been added to provide the concept of "compositions" of the previously claimed conjugates. Compositions of conjugates are provided in the first sentence of Paragraph 0121.

As support for the changes is found in the application as filed, no new matter is introduced by the entry of the above-identified changes. The changes to the claims are made for clarification purposes only should not be interpreted as acquiescence in any claim rejection.

### III. The Restriction Requirement

Applicants continue to reserve their right to petition the Commissioner to review the requirement for restriction, deferring the filing of such petition until after final action on or allowance of the claims, but not later than appeal. See 37 C.F.R. §1.144.

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#### **IV. The Rejection Under 35 U.S.C. §102(b)**

The Examiner maintained the rejection of claims 1-7, 12-15, 17-22, 24, and 26-30 under 35 U.S.C. §102(b) as allegedly being anticipated by Minamino et al. (U.S. Patent No. 6,037,452). Ostensibly, the Examiner has taken the position that each and every element of the rejected claims can be found in Minamino et al.

The rejection is respectfully traversed in view of the following remarks.

The standard for anticipation was provided in a previous response by Applicants.

Minamino et al. teaches "structurally useful" modified Factor VIII species as "those containing polyalkylene glycol added to about 50-70% of amino groups." As has been previously pointed out by Applicants, the addition of polyalkylene glycol to about 50-70% of the amino groups associated with native Factor VIII necessarily teaches a conjugate comprising about 79-110 polyalkylene glycol polymers (given the 158 amine-containing lysine residues in this protein). In contrast, Applicants claim a conjugate comprising one, two or three water-soluble polymers covalently attached to a Factor VIII moiety.

Applicants further emphasize Minamino et al.'s teaching of 2,4-bis(methoxypolyoxy-ethylene)-6-traizine-modified Factor VIII in which the polyoxyethylene moiety has a molecular weight of 5000 or more. See Minamino et al. at column 6, lines 61-64. To the extent that "5000 or more" can even be considered a range (given this phrase's infinite or near infinite set of values), such a range lacks "sufficient specificity" to render Applicants' claim reciting (among other things) a nominal average molecular weight in the range of from 6,000 to 150,000 Daltons as unpatentable under 35 U.S.C. 102(a). In particular, each of the examples provided in Minamino et al. lacks any description of the polyethylene glycol molecular weight -- much less a molecular weight falling within Applicant's claimed range.

Consequently, for at least these reasons, Minamino et al. does not anticipate the rejected claims. Reconsideration and removal of the rejection under 35 U.S.C. 102(b) for at least the reasons provided above is respectfully requested.

#### **V. The First Rejection Under 35 U.S.C. §103(a)**

The Examiner has maintained the rejection of claims 1, 3-4 and 8-10 under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Davis et al. (U.S. Patent No. 4,179,337).

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The rejection is respectfully traversed in view of the following remarks.

The standard for establishing a *prima facie* case of obviousness was provided in a previous response by Applicants.

As set forth in Section IV, Applicants have shown how the pending claims distinguish over Minamino et al.

In addition, Davis et al. does not cure the deficiencies of Minamino et al. As previously pointed out by Applicants, Davis et al. describes utilization of "between 10 and 100, suitably between 15 to 50 moles of polymer per mole of polypeptide." See Davis et al. at column 3, lines 10-13. Further, Davis et al. describes compositions comprising between 10 and 100 polymer moieties per molecule of insulin (Davis et al., claim 5) and enzyme (Davis et al., claim 19). Clearly, Davis et al. does not describe conjugates comprising one, two or three water-soluble polymers covalently attached to a Factor VIII moiety, wherein each water-soluble polymer has a nominal average molecular weight in the range of 6,000 Daltons to 150,000 Daltons

Consequently, as neither Minamino et al. nor Davis et al. teaches or suggests all the claim elements, the third prong of *prima facie* obviousness fails to be satisfied. As a result, the obviousness rejection of claims 1, 3-4 and 8-10 under 35 U.S.C. §103(a) is unsustainable. Reconsideration and withdrawal of the rejection for at least the reasons provided above is respectfully requested.

#### VI. The Second Rejection Under 35 U.S.C. §103(a)

The Examiner has maintained the rejection of claims 1, 3-4 and 8-11 under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Greenwald (U.S. Patent No. 5,298,643).

The rejection is respectfully traversed in view of the following remarks.

The standard for establishing a *prima facie* case of obviousness was provided in a previous response by Applicants.

As set forth in Section IV, Applicants have shown how the pending claims distinguish over Minamino et al.

Greenwald describes reacting aryl imidate activated polyalkylene oxide with  $\epsilon$ -NH<sub>2</sub> moieties of lysines and that "the degree of conjugation is limited only by the number of  $\epsilon$ -NH<sub>2</sub> moieties of lysines." See Greenwald at column 8, lines 4-15. Again, given the 158 amine-containing lysine

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residues in native Factor VIII (see Paragraph 0107) it is clear that Greenwald describes compositions of conjugates wherein each conjugate has a relatively large number of polymers attached to a protein or polypeptide. Thus, Greenwald neither discloses nor suggests conjugates comprising one, two or three water-soluble polymers covalently attached to a Factor VIII moiety, wherein each water-soluble polymer has a nominal average molecular weight in the range of from 6,000 Daltons to 150,000 Daltons.

Consequently, as neither Minamino et al. nor Greenwald teaches or suggests all the claim elements, the third prong of *prima facie* obviousness fails to be satisfied. As a result, the obviousness rejection of claims 1, 3-4 and 8-11 under 35 U.S.C. §103(a) is unsustainable. Reconsideration and withdrawal of the rejection for at least the reasons provided above is respectfully requested.

#### VII. The Third Rejection Under 35 U.S.C. §103(a)

The Examiner has maintained the rejection of claims 1, 14 and 16 under 35 U.S.C. §103(a) as allegedly being unpatentable over Röstin et al. [Röstin et al. (2000) *Bioconjugate Chem.* 11:387-396] in view of Greenwald (U.S. Patent No. 5,298,643).

The standard for establishing a *prima facie* case of obviousness was provided in a previous response by Applicants.

Röstin et al. describes the preparation of several compositions of conjugates. Each of Röstin et al.'s described compositions of conjugates is prepared using polymers having molecular weights of 3,000 Daltons or 5,000 Daltons. Thus, Röstin et al. neither discloses nor suggests conjugates comprising one, two or three water-soluble polymers covalently attached to a Factor VIII moiety, wherein each water-soluble polymer has a nominal average molecular weight in the range of from 6,000 Daltons to 150,000 Daltons.

Greenwald, which was discussed in Section VI, does not cure the deficiencies of Röstin et al. For example, the feature of one, two or three water-soluble polymers -- each having a nominal average molecular weight in the range of from 6,000 Daltons to 150,000 Daltons -- is neither disclosed nor suggested in Greenwald.

Consequently, as neither Röstin et al. nor Greenwald teach or suggest all the claim elements, the third prong of *prima facie* obviousness fails to be satisfied. As a result, the obviousness rejection of claims 1, 14 and 16 under 35 U.S.C. §103(a) is unsustainable.

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Reconsideration and withdrawal of the rejection for at least the reasons provided above is respectfully requested.

#### **VIII. The Fourth Rejection Under 35 U.S.C. §103(a)**

The Examiner has maintained the rejection of claims 1, 23 and 25 under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Longenecker et al. (U.S. Patent No. 4,994,439).

The rejection is respectfully traversed in view of the following remarks.

The standard for establishing a *prima facie* case of obviousness was provided in a previous response by Applicants.

As set forth in Section IV, Applicants have shown how the pending claims distinguish over Minamino et al.

Longenecker et al. is completely silent with respect to compositions containing any conjugates.

Thus, as neither Minamino et al. nor Longenecker et al. teaches or suggests all the claim elements, the third prong of *prima facie* obviousness fails to be satisfied. As a result, the obviousness rejection of claims 1, 23 and 25 under 35 U.S.C. §103(a) is unsustainable. Reconsideration and withdrawal of the rejection for at least the reasons provided above is respectfully requested.

#### **IX. Conclusion**

In view of the foregoing, Applicants submit that the pending claims satisfy the requirements of patentability and are therefore in condition for allowance. Reconsideration and withdrawal of all objections and rejections is respectfully requested and a prompt mailing of a Notice of Allowance is earnestly solicited.

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If a telephone conference would expedite the prosecution of the subject application, the Examiner is requested to call the undersigned at (650) 620-5506.

Respectfully submitted,  
Nektar Therapeutics

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